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## Case Report

# Oxandrolone Improves Height Velocity and BMI in Patients with Cystic Fibrosis

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**Objective.** To evaluate the effectiveness of oxandrolone in improving the nutritional status and linear growth of pediatric patients with cystic fibrosis (CF). **Methods.** Medical records of patients with CF treated with oxandrolone were reviewed for height z score, height velocity (HV), BMI z score, weight velocity (WV), Tanner stage, pulmonary function, liver enzyme levels, and any reported adverse events. Data were compared before (pre-Ox) and after (Ox) oxandrolone using a paired *t*-test. **Results.** 5 subjects (ages 8.5–14.5 years) were treated with oxandrolone 2.5 mg daily for 8–38 months. After 8–12 months of treatment, there was a statistically significant improvement in HV (pre-Ox =  $5.3 \pm 1.4$  cm/yr, Ox =  $8.3 \pm 1.2$  cm/yr,  $P < .01$ ) and BMI z score (pre-Ox =  $-0.61 \pm 1.04$ , Ox =  $-0.30 \pm 0.86$ ,  $P = .02$ ). Both height z score (pre-Ox =  $-1.64 \pm 0.63$ , Ox =  $-1.30 \pm 0.49$ ,  $P = .057$ ) and WV (pre-Ox =  $4.2 \pm 3.7$  kg/yr, Ox =  $6.8 \pm 1.0$  kg/yr,  $P = .072$ ) showed beneficial trends that did not reach statistical significance. No adverse events were reported. **Conclusions.** In this brief clinical report, oxandrolone improved the HV and BMI z score in patients with CF. Larger studies are needed to determine if oxandrolone is an effective, safe, and affordable option to stimulate appetite, improve weight gain, and promote linear growth in patients with CF.

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## 1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder that features chronic pulmonary disease, pancreatic insufficiency, and other organ involvement. Patients with CF often have malnutrition and short stature. According to the Cystic Fibrosis Foundation Patient Registry 2007 Annual Data Report, 21% of patients with CF had weight less than the 10th percentile, while 13% had height below the 5th percentile [1]. Malnutrition and poor growth velocity are associated with declining pulmonary function, morbidity, and mortality [2–5]. Steady improvements in nutritional status are associated with greater pulmonary function [6], and evidence-based practice recommendations strongly advise close monitoring of growth and nutritional status as well as aggressive nutritional intervention for patients with CF [7].

Multiple agents have been used to stimulate appetite and growth in patients with CF, but their utility has been

limited due to side effects (such as adrenal suppression with megestrol) or cost (such as growth hormone). Oxandrolone is a relatively weak androgen that stimulates appetite and promotes linear growth and has been safely used to treat a variety of conditions associated with wasting, poor weight gain, or short stature [8]. Furthermore, oxandrolone is an attractive option in growing children because it cannot be aromatized to estrogen, and therefore estrogen-dependent advancement of the bone age is minimized. To our knowledge, there are no reports in the literature of the use of oxandrolone in patients with CF.

For the past 4 years, children with CF referred to our endocrine clinic for persistent growth concerns in spite of other nutrition-augmentation strategies have occasionally been treated with oxandrolone. This retrospective analysis evaluates the effectiveness of oxandrolone in improving the weight gain and linear growth of these patients.

TABLE 1: Patient characteristics at the initiation of oxandrolone treatment.

| Patient | Age<br>(years) | Gender<br>(M/F) | Pancreatic<br>Insufficiency<br>(Y/N) | Tanner<br>Stage | Height z<br>score | Height<br>velocity<br>(cm/yr) | BMI z<br>score | Weight<br>velocity<br>(kg/yr) | FEV1 (%)<br>predicted) | FEV/FVC |
|---------|----------------|-----------------|--------------------------------------|-----------------|-------------------|-------------------------------|----------------|-------------------------------|------------------------|---------|
| 1       | 8.5            | F               | Y                                    | 1               | -2.39             | 5.8                           | 0.82           | 6.6                           | 118                    | 90      |
| 2       | 11.9           | F               | Y                                    | 1               | -0.74             | 5.0                           | -1.39          | -0.1                          | 91                     | 90      |
| 3       | 14.5           | M               | Y                                    | 4               | -1.97             | 7.4                           | -1.03          | 8.8                           | 70                     | 78      |
| 4       | 12.6           | M               | Y                                    | 1               | -1.32             | 4.6                           | 0.13           | 4.2                           | 95                     | 82      |
| 5       | 12.0           | M               | Y                                    | 1               | -1.76             | 3.6                           | -1.59          | 1.4                           | 67                     | 78      |
| Mean    | 11.9           |                 |                                      |                 | -1.64             | 5.3                           | -0.61          | 4.18                          | 88.2                   | 83.6    |
| SD      | 2.2            |                 |                                      |                 | 0.63              | 1.4                           | 1.04           | 3.65                          | 20.8                   | 6.1     |

## 2. Materials and Methods

We reviewed the medical records of all patients in our endocrine clinic with CF who were treated with oxandrolone for at least 8 months between January of 2005 and October of 2008. Medical records were reviewed to determine height z score, height velocity (HV), body mass index (BMI) z score, and weight velocity (WV). Additional information obtained included age, Tanner stage, pulmonary function, liver enzyme levels, and any reported adverse events. This retrospective chart review was approved by the University of Wisconsin Human Subjects Committee.

Patients from the University of Wisconsin CF Clinic are referred to the endocrine clinic due to poor nutritional status and/or poor height gain, particularly when the growth is well below the clinic reference population (see data in results below). There were no predetermined nutritional cutoffs or pubertal stage for the initiation of oxandrolone. All subjects were treated with 2.5 mg of oxandrolone.

Height was measured on a wall-mounted stadiometer to the nearest 0.1 cm. Weight was measured on a calibrated beam balance platform scale to the nearest 0.1 kg. Weight and height measurements were used to calculate the BMI z score, which is the preferred method (as opposed to percentage of ideal body weight) for monitoring nutritional status in patients with cystic fibrosis [7, 9, 10]. Pretreatment height/weight velocities were calculated using the measurement at initiation of oxandrolone and the measurement 4–8 months prior to initiation of oxandrolone. Posttreatment height/weight velocities were calculated using the measurement at initiation of oxandrolone and the measurement 8–12 months after initiation of oxandrolone. Lung function parameters were measured with a Jaeger Masterscreen spirometer in accordance with the American Thoracic Society guidelines [11]. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were determined and the results expressed as percentages of the reference values of Wang et al. [12].

Descriptive statistics are expressed as mean  $\pm$  SD or frequency with a percentage. Data were compared before (pre-Ox) and after (Ox) initiation of oxandrolone using a paired *t*-test.

## 3. Results

Five subjects (3 boys and 2 girls) were identified. The Table 1 lists the baseline characteristics for each subject. The subjects ranged from 8.5 to 14.5 years in age and were treated with oxandrolone for 8–38 months. All subjects were prescribed oral oxandrolone 2.5 mg daily. All subjects had pancreatic insufficiency. At the start of oxandrolone therapy, four subjects had Tanner 1 genitalia or breasts, and one male patient had Tanner 4 genitalia.

The five subjects had a mean height z score of  $-1.64$  and a mean BMI z score of  $-0.61$ . As a comparison, we obtained data for patients between the ages of 11 and 14 seen between January 1, 2004 and December 31, 2008 in our CF Clinic. For females ( $n = 21$ ), the average height z score was  $-0.14$  and the average BMI z score was  $0.04$ . For males ( $n = 37$ ), the average height z score was  $-0.28$  and the average BMI z score was  $-0.19$ . Therefore, the subjects' poor weight and/or height gain was validated by a comparison to other patients in the CF clinic.

Figure 1 illustrates the anthropometric changes seen with oxandrolone. After 8–12 months of treatment, there was a statistically significant improvement in HV (pre-Ox =  $5.3 \pm 1.4$  cm/yr, Ox =  $8.3 \pm 1.2$  cm/yr,  $P < .01$ ) and BMI z score (pre-Ox =  $-0.61 \pm 1.04$ , Ox =  $-0.30 \pm 0.86$ ,  $P = .02$ ). Both height z score (pre-Ox =  $-1.64 \pm 0.63$ , Ox =  $-1.30 \pm 0.49$ ,  $P = .057$ ) and WV (pre-Ox =  $4.2 \pm 3.7$  kg/yr, Ox =  $6.8 \pm 1.0$  kg/yr,  $P = .072$ ) showed beneficial trends that did not reach statistical significance. When the subject with Tanner 4 genitalia (#3) was removed from the analysis, there was still a significant improvement in HV and BMI z score.

There was no significant change in pulmonary function or liver enzyme levels, and no adverse events were reported. Neither female subject experienced hirsutism, clitoromegaly, or any evidence of hyperandrogenism. One female subject (#2) remained on oxandrolone for a total of 38 months (beyond the time frame used to calculate the anthropometric data shown above) and had normal pubertal progression and menarche. One subject (#4) had CF-related liver disease with mildly elevated liver enzyme tests at the initiation of oxandrolone, and his liver enzyme tests improved slightly while on oxandrolone. Two subjects (#4 and #5) had previously been on mirtazapine to stimulate appetite.

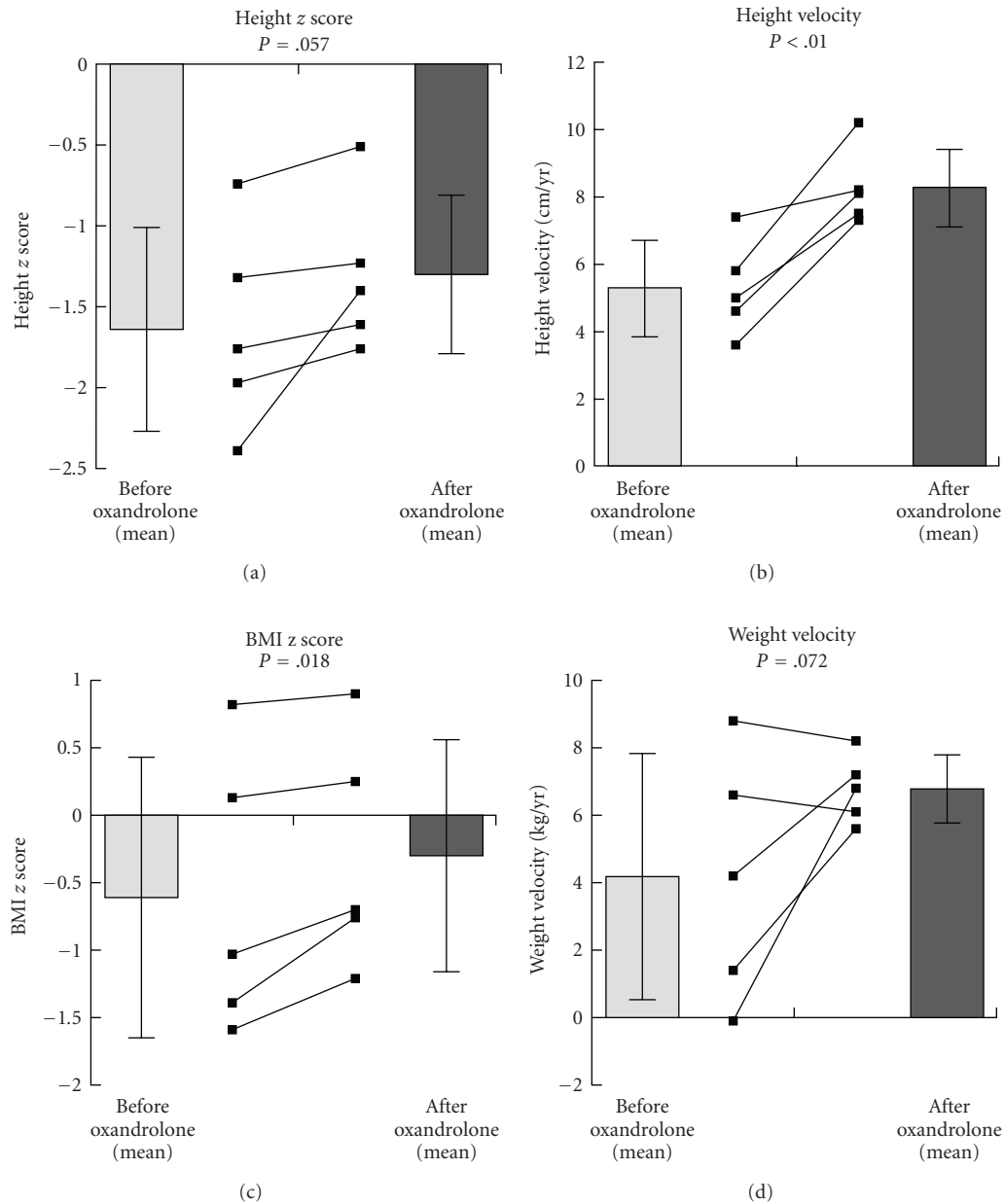


FIGURE 1: Anthropometric data for subjects ( $n = 5$ ) before and after initiation of oxandrolone.

#### 4. Discussion

In this brief clinical report, we describe 5 children with CF who received oxandrolone for at least 8–12 months. All 5 children had height z scores well below the clinic average, and 3 of the subjects had BMI z scores below the clinic average. Oxandrolone improved the height velocity and BMI z score in these patients with CF and showed a trend towards significance in weight velocity and height z score. No significant changes in pulmonary function or liver enzyme tests were appreciated.

Optimizing linear growth and weight gain is critically important in the care of children with CF. A comprehensive

practice recommendation found significant evidence that weight-for-age, height-for-age, and weight-for-height percentiles are associated with improved pulmonary function and survival [7]. It is important to emphasize that a “weight only” approach will not necessarily result in improved height and/or lung function. Lai et al. noted that poor linear growth can occur independent of weight [13], and some children with CF have a linear height that is more adversely affected than would be suggested by the degree of malnutrition [14]. Therefore, increasing weight alone may not fully address the short stature that is commonly seen in patients with CF. Ideally, a growth-promoting agent in patients with CF would improve both weight and height.

Multiple appetite stimulants have been studied in patients with CF, including megestrol, cyproheptadine, atypical antipsychotics, and antidepressants [15]. Megestrol has been shown to improve weight in patients with CF, but side effects include adrenal suppression, glucose intolerance, and diabetes [16–18]. More importantly, the nonanabolic glucocorticoid actions of megestrol promote accumulation of fat mass in excess of lean body mass.

In order to stimulate appetite but to also improve body composition, anabolic agents have been used in patients with CF. Growth hormone (GH) is a potent anabolic agent that has the capacity to improve the nutritional status of patients with CF. Several studies have shown that GH in children with CF leads to improved height and weight [19–23], while one study found only an improvement in height [24]. While there were theoretical concerns of glucose intolerance with the use of GH, no study of GH in patients with CF has described this complication. There are a few disadvantages of GH. A minor concern is the use of daily injections, while a major concern is cost. The mean average wholesale price for GH, based on 6 different GH preparations, is \$66.60 per mg, and therefore at an expected dose of 0.30 mg/kg/week, the estimated annual cost of GH for the 5 subjects in this paper would range from \$28,500 (subject #1) to \$43,900 (subject #3).

Insulin is an anabolic hormone that can improve BMI in patients with CF-related diabetes, but insulin has not been studied in patients without CF-related diabetes and carries the obvious risk of hypoglycemia.

Several articles from the 1960s describe the use of older anabolic steroids (stanozolol, methandrostenolone, and norethandrolone) in patients with CF [25–27]. While these studies reported some modest improvements in weight and height gain (as well as an improvement in “cheerfulness” [27]), in general these early anabolic steroids had very high androgenic side effect profiles that limited their utility.

Oxandrolone is a weak oral androgen taken once daily that has marked anabolic properties with minimal androgenic effects [8]. Oxandrolone is clinically efficacious across a variety of diseases associated with catabolism and wasting and is FDA-approved as adjunctive therapy for weight loss due to catabolic conditions in both adults and children [8]. Oxandrolone has also been used as a height-promoting agent. Prior to the availability of recombinant human GH, oxandrolone was commonly used to increase growth velocity in girls with Turner Syndrome [29, 30]. Oxandrolone has also been shown to increase growth velocity (but not eventual adult height) in boys with constitutional delay of growth and puberty [31]. Oxandrolone cannot be aromatized to estrogen, which minimizes advancement of the bone age. Oxandrolone is also relatively cheap. The average wholesale price of a 2.5 mg tablet of oxandrolone is \$5.53, which translates to an annual cost of approximately \$2,000, substantially less than the cost of GH.

While oxandrolone is generally well-tolerated, there are important potential side effects to consider. Oxandrolone can cause transient elevations in liver transaminases [8], which could be a factor in patients with or at risk for CF-related liver disease. Importantly, however, oxandrolone does not appear to cause the severe hepatotoxic effects associated with other

anabolic steroids [8]. Secondly, while oxandrolone has a high anabolic to androgenic ratio [28], girls in particular may experience dose-dependent androgenic side effects, such as increase in body hair, deepened voice, or clitoral hypertrophy [30]. In a review of the efficacy and safety of oxandrolone used at modest dosages (e.g., usually 2.5–3.75 mg/day), very few studies report detectable androgenic side effects, even in studies that included women and girls [8]. Nonetheless, it would be prudent to monitor closely for signs of excess androgen in girls treated with oxandrolone.

This retrospective, noncontrolled report of a small number of subjects has intrinsic limitations. Changes in clinical and anthropometric outcomes may be confounded by the disease itself (which waxes and wanes) or by early puberty. The duration of the study was also relatively short, which makes it difficult to determine if oxandrolone had a positive effect on pulmonary function tests or a negative effect on liver enzyme tests. A randomized controlled trial would help determine if oxandrolone, compared to an appropriate control group, improves the nutritional status and/or lung function in patients with CF.

## 5. Conclusion

In this small retrospective exploratory study, oxandrolone safely and effectively improved the height velocity and BMI z score in patients with CF. Larger prospective studies are needed to determine more conclusively whether oxandrolone should be considered an effective, safe, and affordable option to stimulate appetite and promote growth in patients with CF.

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